Complete Summary

GUIDELINE TITLE

Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines 2002.

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2002 May 10;51(RR-6):42-8.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Bacterial vaginosis
- Trichomoniasis
- Vulvovaginal candidiasis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine

Obstetrics and Gynecology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Managed Care Organizations
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To update the 1998 Guidelines for Treatment of Sexually Transmitted Diseases (MMWR 1998;47[No. RR-1])
- To assist physicians and other health-care providers in preventing and treating sexually transmitted diseases (STDs)
- To present updated recommendations for the diagnosis and management of bacterial vaginosis, trichomoniasis, and vulvovaginal candidiasis

TARGET POPULATION

Women with suspected or confirmed bacterial vaginosis, trichomoniasis, and vaginal candidiasis (including pregnant women and women infected with human immunodeficiency virus [HIV]) and their sex partners

INTERVENTIONS AND PRACTICES CONSIDERED

Note from the National Guideline Clearinghouse and the Centers for Disease Control and Prevention: These guidelines focus on the treatment and counseling of individual patients and do not address other community services and interventions that are important in sexually transmitted disease/human immunodeficiency virus (STD/HIV) prevention.

Diagnosis

1. Microscopic examination of fresh vaginal discharge
2. Vaginal pH
3. Gram stain of vaginal discharge
4. Culture for Candida albicans and Trichomonas vaginalis
5. Evaluation of odor of vaginal discharge after addition of 10% potassium hydroxide (KOH) (whiff test)
6. Evaluation of signs and symptoms

Treatment/Management

1. Metronidazole (oral, topical cream, or gel)
2. Clindamycin (oral, topical cream, or gel)

3. Topical (intravaginal) antifungals such as butoconazole, clotrimazole, miconazole, nystatin, tioconazole, and terconazole
4. Oral ketoconazole, itraconazole, and fluconazole
5. Follow-up
6. Management of sex partners
7. Special considerations in pregnant and immunocompromised (e.g., HIV-infected) women and in women with allergies or intolerance to antifungal treatment

MAJOR OUTCOMES CONSIDERED

- Microbiologic cure
- Alleviation of signs and symptoms
- Prevention of sequelae
- Prevention of transmission

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Subjective Review

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Beginning in 2000, Centers for Disease Control and Prevention (CDC) personnel and professionals knowledgeable in the field of sexually transmitted diseases (STDs) systematically reviewed literature (i.e., published abstracts and peer-reviewed journal articles) concerning each of the major STDs, focusing on information that had become available since publication of the 1998 Guidelines for

Treatment of Sexually Transmitted Diseases. Background papers were written and tables of evidence constructed summarizing the type of study (e.g., randomized controlled trial or case series), study population and setting, treatments or other interventions, outcome measures assessed, reported findings, and weaknesses and biases in study design and analysis. A draft document was developed on the basis of the reviews.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse and the Centers for Disease Control and Prevention: When more than one therapeutic regimen is recommended, the sequence is alphabetized unless the choices for therapy are prioritized based on efficacy, convenience, or cost. For sexually transmitted diseases (STDs) with more than one recommended regimen, almost all regimens have similar efficacy and similar rates of intolerance or toxicity unless otherwise specified.

Vaginal infection is usually characterized by a vaginal discharge or vulvar itching and irritation; a vaginal odor may be present. The three diseases most frequently associated with vaginal discharge are trichomoniasis (caused by T. vaginalis), bacterial vaginosis (caused by a replacement of the normal vaginal flora by an overgrowth of anaerobic microorganisms, mycoplasmas, and Gardnerella vaginalis), and candidiasis (usually caused by Candida albicans). Mucopurulent cervicitis (MPC) caused by C. trachomatis or N. gonorrhoeae can sometimes cause vaginal discharge. Although vulvovaginal candidiasis and bacterial vaginosis are not usually transmitted sexually, they are included in this section because these infections are often diagnosed in women being evaluated for STDs.

The cause of vaginal infection can be diagnosed by pH and microscopic examination of the discharge. The pH of the vaginal secretions can be determined by narrow-range pH paper for the elevated pH (>4.5) typical of bacterial vaginosis (BV) or trichomoniasis. Discharge can be examined by diluting one sample in one to two drops of 0.9% normal saline solution on one slide and a second sample in 10% potassium hydroxide (KOH) solution. An amine odor detected before or immediately after applying potassium hydroxide suggests BV. A cover slip is placed on the slides, and they are examined under a microscope at low- and high-dry power. The motile T. vaginalis or the clue cells of BV usually are identified easily in the saline specimen. The yeast or pseudohyphae of Candida species are more easily identified in the potassium hydroxide specimen. However, their absence does not preclude candidal or trichomonal infection, because several studies have demonstrated the presence of these pathogens by using polymerase chain reaction (PCR) after a negative microscopic exam. The presence of objective signs of external vulvar inflammation in the absence of vaginal pathogens, along with a minimal amount of discharge, suggests the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva. Culture for T. vaginalis is more sensitive than microscopic examination. Laboratory testing fails to identify the cause of vaginitis among a minority of women.

Bacterial Vaginosis

BV is a clinical syndrome resulting from replacement of the normal hydrogen peroxide (H_2O_2)-producing Lactobacillus sp. in the vagina with high concentrations of anaerobic bacteria (e.g., Prevotella sp. and Mobiluncus sp.), G. vaginalis, and Mycoplasma hominis. BV is the most prevalent cause of vaginal discharge or malodor; however, up to 50% of women with BV may not report symptoms of BV. The cause of the microbial alteration is not fully understood. BV is associated with having multiple sex partners, douching, and lack of vaginal lactobacilli; it is unclear whether BV results from acquisition of a sexually transmitted pathogen. Women who have never been sexually active are rarely affected. Treatment of the male sex partner has not been beneficial in preventing the recurrence of BV.

Diagnostic Considerations

BV can be diagnosed by the use of clinical or Gram-stain criteria. Clinical criteria require three of the following symptoms or signs:

- a homogeneous, white, noninflammatory discharge that smoothly coats the vaginal walls
- the presence of clue cells on microscopic examination
- a pH of vaginal fluid >4.5
- a fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test)

When a Gram stain is used, determining the relative concentration of the bacterial morphotypes characteristic of the altered flora of BV is an acceptable laboratory method for diagnosing BV. Culture of G. vaginalis is not recommended as a diagnostic tool because it is not specific. However, a deoxyribonucleic acid (DNA) probe based test for high concentrations of G. vaginalis [Affirm™ VP III, manufactured by Becton Dickinson, Sparks, Maryland] may have clinical utility. Cervical Pap tests have limited clinical utility for the diagnosis of BV because of

low sensitivity. Other commercially available tests that may be useful for the diagnosis of BV include a card test for the detection of elevated pH and trimethylamine [FemExam(R) test card, manufactured by Cooper Surgical, Shelton, Connecticut] and prolineaminopeptidase [Pip Activity TestCard™ manufactured by Litmus Concepts, Inc., Santa Clara, California].

Treatment

The established benefits of therapy for BV in non-pregnant women are to a) relieve vaginal symptoms and signs of infection and b) reduce the risk for infectious complications after abortion or hysterectomy. Other potential benefits include the reduction of other infectious complications (e.g., human immunodeficiency virus [HIV] and other STDs). All women who have symptomatic disease require treatment.

BV during pregnancy is associated with adverse pregnancy outcomes, including premature rupture of the membranes, preterm labor, preterm birth, and postpartum endometritis. The established benefit of therapy for BV in pregnant women is to relieve vaginal symptoms and signs of infection. Additional potential benefits of therapy include a) reducing the risk for infectious complications associated with BV during pregnancy and b) reducing the risk for other infections (e.g., other STDs or HIV). The results of several investigations indicate that treatment of pregnant women who have BV and who are at high risk for preterm delivery (i.e., those who previously delivered a premature infant) may reduce the risk for prematurity. Therefore, high-risk pregnant women who have asymptomatic BV may be evaluated for treatment.

The bacterial flora that characterizes BV have been recovered from the endometria and salpinges of women who have pelvic inflammatory disease (PID). BV has been associated with endometritis, pelvic inflammatory disease, and vaginal cuff cellulitis after invasive procedures, including endometrial biopsy, hysterectomy, hysterosalpingography, placement of an intrauterine device (IUD), cesarean section, and uterine curettage. The results of two randomized controlled trials indicated that treatment of BV with metronidazole substantially reduced postabortion pelvic inflammatory disease. Three trials that evaluated the use of anaerobic antimicrobial coverage (metronidazole) for routine operative prophylaxis before abortion and seven trials that evaluated this additional coverage for women undergoing hysterectomy found a substantial reduction (range: 10%--75%) in post-operative infectious complications. Because of the increased risk for postoperative infectious complications associated with BV, some specialists recommend that before performing surgical abortion or hysterectomy, providers screen and treat women with BV in addition to providing routine prophylaxis. However, more information is needed before recommending treatment of asymptomatic BV before other invasive procedures.

Recommended Regimens

- Metronidazole 500 mg orally twice a day for 7 days

  OR

- Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days

  OR

- Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days

Note: Patients should be advised to avoid consuming alcohol during treatment with metronidazole and for 24 hours thereafter. Clindamycin cream and ovules are oil-based and might weaken latex condoms and diaphragms. Refer to condom product labeling for additional information.

The recommended metronidazole regimens are equally efficacious. The vaginal clindamycin cream appears less efficacious than the metronidazole regimens. The alternative regimens have lower efficacy for BV.

Alternative Regimens

- Metronidazole 2 g orally in a single dose

  OR

- Clindamycin 300 mg orally twice a day for 7 days

  OR

- Clindamycin ovules 100 g intravaginally once at bedtime for 3 days

One randomized trial evaluating the clinical equivalency of intravaginal metronidazole gel 0.75% once daily versus twice daily found similar cure rates 1 month after therapy. One randomized trial that evaluated the equivalency of clindamycin cream and clindamycin ovules found that cure rates did not differ significantly. Metronidazole 2 g single-dose therapy is an alternative regimen because of its lower efficacy for treatment of BV. Although the Food and Drug Administration (FDA) has approved metronidazole 750-mg extended release tablets once daily for 7 days, no data have been published on the clinical equivalency of this regimen with other regimens.

Studies are currently underway to evaluate the efficacy of vaginal lactobacilli suppositories in addition to oral metronidazole for the treatment of BV. No data support the use of non-vaginal lactobacilli or douching for the treatment of BV.

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because recurrence of BV is not unusual, women should be advised to return for additional therapy if symptoms recur. Another recommended treatment regimen may be used to treat recurrent disease. No long-term maintenance regimen with any therapeutic agent is recommended.

Management of Sex Partners

The results of clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner(s). Therefore, routine treatment of sex partners is not recommended.

Special Considerations

Allergy or Intolerance to the Recommended Therapy

Clindamycin cream or oral clindamycin is preferred in case of allergy or intolerance to metronidazole. Metronidazole gel can be considered for patients who do not tolerate systemic metronidazole, but patients allergic to oral metronidazole should not be administered metronidazole vaginally.

Pregnancy

All symptomatic pregnant women should be tested and treated. BV has been associated with adverse pregnancy outcomes (e.g., premature rupture of the membranes, chorioamnionitis, preterm labor, preterm birth, postpartum endometritis, and post-cesarean wound infection). Some specialists prefer using systemic therapy to treat possible subclinical upper genital tract infections among women at low risk for preterm delivery (i.e., those who have no history of delivering an infant before term). Existing data do not support the use of topical agents during pregnancy. Evidence from three trials suggests an increase in adverse events (e.g., prematurity and neonatal infections), particularly in newborns, after use of clindamycin cream. Multiple studies and meta-analyses have not demonstrated a consistent association between metronidazole use during pregnancy and teratogenic or mutagenic effects in newborns.

Recommended Regimens

- Metronidazole 250 mg orally three times a day for 7 days

  OR

- Clindamycin 300 mg orally twice a day for 7 days

Because treatment of BV in asymptomatic pregnant women at high risk for preterm delivery (i.e., those who have previously delivered a premature infant) with a recommended regimen has reduced preterm delivery in three of four randomized controlled trials, some specialists recommend the screening and treatment of these women. However, the optimal treatment regimens have not been established. The screening (if conducted) and treatment should be performed at the first prenatal visit.

The two trials that examined the use of metronidazole during pregnancy used the 250-mg regimen; the recommended regimen for BV in nonpregnant women is 500 mg twice daily. Some specialists also recommend this higher dose for treatment of pregnant women. In one published study, women with BV were treated at 19 weeks with a regimen of an initial dose of 2 g, followed by a 2-g dose 2 days

later; the regimen was repeated 4 weeks later. This regimen was not effective in reducing preterm birth in any group of women.

Data are conflicting regarding whether treatment of asymptomatic pregnant women who are at low risk for preterm delivery reduces adverse outcomes of pregnancy. Several unpublished trials have evaluated screening and treatment for BV among asymptomatic low-risk pregnant women in the first or early second trimester. One trial, using oral clindamycin, demonstrated a reduction in spontaneous preterm birth; another indicated a reduction in postpartum infectious complications.

Follow-Up of Pregnant Women

Treatment of BV in asymptomatic pregnant women who are at high risk for preterm delivery might prevent adverse pregnancy outcomes. Therefore, a follow-up evaluation 1 month after completion of treatment should be considered to evaluate whether therapy was effective.

HIV Infection

Patients who have BV and also are infected with HIV should receive the same treatment regimen as those who are HIV-negative.

Trichomoniasis

Trichomoniasis is caused by the protozoan T. vaginalis. Most men who are infected with T. vaginalis do not have symptoms; others have nongonococcal urethritis. Many infected women have symptoms characterized by a diffuse, malodorous, yellow-green discharge with vulvar irritation. However, some women have minimal or no symptoms. Diagnosis of vaginal trichomoniasis is usually performed by microscopy of vaginal secretions, but this method has a sensitivity of only about 60%--70%. Culture is the most sensitive commercially available method of diagnosis. No FDA-approved polymerase chain reaction test for T. vaginalis is available in the United States, but such testing may be available from commercial laboratories that have developed their own polymerase chain reaction tests.

Recommended Regimen

- Metronidazole 2 g orally in a single dose.

Alternative Regimen

- Metronidazole 500 mg twice a day for 7 days.

The nitroimidazoles comprise the only class of drugs useful for the oral or parenteral therapy of trichomoniasis. Of these, only metronidazole is readily available in the United States and approved by the FDA for the treatment of trichomoniasis. In randomized clinical trials, the recommended metronidazole regimens have resulted in cure rates of approximately 90%--95%; ensuring treatment of sex partners might increase this rate. Treatment of patients and sex

partners results in relief of symptoms, microbiologic cure, and reduction of transmission. Metronidazole gel has been approved for treatment of BV. However, like other topically applied antimicrobials that are unlikely to achieve therapeutic levels in the urethra or perivaginal glands, it is considerably less efficacious for treatment of trichomoniasis (≤50%) than oral preparations of metronidazole. Therefore, metronidazole gel is not recommended for use. Several other topically applied antimicrobials have occasionally been used for treatment of trichomoniasis, but it is unlikely that these preparations have greater efficacy than metronidazole gel.

Follow-Up

Follow-up is unnecessary for men and women who become asymptomatic after treatment or who are initially asymptomatic. Certain strains of T. vaginalis can have diminished susceptibility to metronidazole; however, infections caused by most of these organisms respond to higher doses of metronidazole. If treatment failure occurs with either regimen, the patient should be re-treated with metronidazole 500 mg twice a day for 7 days. If treatment failure occurs again, the patient should be treated with a single, 2-g dose of metronidazole once a day for 3--5 days.

Patients with laboratory-documented infection who do not respond to the 3--5 day treatment regimen and who have not been reinfected should be managed in consultation with a specialist; evaluation of such cases should ideally include determination of the susceptibility of T. vaginalis to metronidazole. Consultation is available from Centers for Disease Control and Prevention (CDC) (tel: 770-488-4115; website: http://www.cdc.gov/std/).

Management of Sex Partners

Sex partners of patients with T. vaginalis should be treated. Patients should be instructed to avoid sex until they and their sex partners are cured (i.e., when therapy has been completed and patient and partner(s) are asymptomatic [in the absence of a microbiologic test of cure]).

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Patients with an immediate-type allergy to metronidazole can be managed by desensitization). Topical therapy with drugs other than nitroimidazoles can be attempted, but cure rates are low (≤50%).

Pregnancy

Vaginal trichomoniasis has been associated with adverse pregnancy outcomes, particularly premature rupture of the membranes, preterm delivery, and low birthweight. Data have not indicated that treating asymptomatic trichomoniasis during pregnancy lessens that association. Women who are symptomatic with trichomoniasis should be treated to ameliorate symptoms.

Women may be treated with 2 g of metronidazole in a single dose. Multiple studies and meta-analyses have not demonstrated a consistent association between metronidazole use during pregnancy and teratogenic or mutagenic effects in infants.

HIV Infection

Patients who have trichomoniasis and also are infected with HIV should receive the same treatment regimen as those who are HIV-negative.

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) usually is caused by C. albicans but occasionally is caused by other Candida sp. or yeasts. Typical symptoms of VVC include pruritus and vaginal discharge. Other symptoms include vaginal soreness, vulvar burning, dyspareunia, and external dysuria. None of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40%--45% will have two or more episodes. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated. Approximately 10%--20% of women will have complicated VVC, suggesting diagnostic and therapeutic considerations.

Classification of vulvovaginal candidiasis (VVC)

Uncomplicated VVC

- Sporadic or infrequent vulvovaginal candidiasis

  OR

- Mild-to-moderate vulvovaginal candidiasis

  OR

- Likely to be C. albicans

  OR

- Non-immunocompromised women

Complicated VVC

- Recurrent vulvovaginal candidiasis

  OR

- Severe vulvovaginal candidiasis

  OR

- Non-albicans candidiasis

  OR

- Women with uncontrolled diabetes, debilitation, or immunosuppression or those who are pregnant

Uncomplicated VVC

Diagnostic Considerations in Uncomplicated VVC

A diagnosis of Candida vaginitis is suggested clinically by pruritus and erythema in the vulvovaginal area; a white discharge may be present. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either a) a wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge demonstrates yeasts or pseudohyphae or b) a culture or other test yields a positive result for a yeast species. Candida vaginitis is associated with a normal vaginal pH ($\leq$4.5). Use of 10% KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Identifying Candida by culture in the absence of symptoms is not an indication for treatment, because approximately 10%--20% of women harbor Candida sp. and other yeasts in the vagina. VVC can occur concomitantly with STDs, and treatment of all pathogens present is warranted. Most healthy women with uncomplicated VVC have no precipitating factors. However, in a minority of women who have asymptomatic Candida colonization, antibiotic use precipitates VVC.

Treatment

Short-course topical formulations (i.e., single dose and regimens of 1--3 days) effectively treat uncomplicated VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80%--90% of patients who complete therapy.

Recommended Regimens

Intravaginal Agents:

- Butoconazole 2% cream 5 g intravaginally for 3 days

  OR

- Butoconazole 2% cream 5 g (Butaconazole1-sustained release), single intravaginal application

  OR

- Clotrimazole 1% cream 5 g intravaginally for 7--14 days

  OR

- Clotrimazole 100 mg vaginal tablet for 7 days

  OR

- Clotrimazole 100 mg vaginal tablet, two tablets for 3 days

  OR

- Clotrimazole 500 mg vaginal tablet, one tablet in a single application

  OR

- Miconazole 2% cream 5 g intravaginally for 7 days (over-the-counter [OTC] preparation)

  OR

- Miconazole 100 mg vaginal suppository, one suppository for 7 days (OTC preparation)

  OR

- Miconazole 200 mg vaginal suppository, one suppository for 3 days (OTC preparation)

  OR

- Nystatin 100,000-unit vaginal tablet, one tablet for 14 days

  OR

- Tioconazole 6.5% ointment 5 g intravaginally in a single application (OTC preparation)

  OR

- Terconazole 0.4% cream 5 g intravaginally for 7 days

  OR

- Terconazole 0.8% cream 5 g intravaginally for 3 days

  OR

- Terconazole 80 mg vaginal suppository, one suppository for 3 days

Oral Agent:

- Fluconazole 150 mg oral tablet, one tablet in single dose

Note: The creams and suppositories in this regimen are oil-based and may weaken latex condoms and diaphragms. Refer to condom product labeling for further information.

Preparations for intravaginal administration of butaconazole, clotrimazole, miconazole, and tioconazole are available over-the-counter (OTC). Self-medication with OTC preparations should be advised only for women who have been diagnosed previously with VVC and who have a recurrence of the same symptoms. Any woman whose symptoms persist after using an OTC preparation or who has a recurrence of symptoms within 2 months should seek medical care. Unnecessary or inappropriate use of OTC preparations is common and can lead to delay of treatment of other etiologies of vulvovaginitis that could result in adverse clinical outcomes.

Follow-Up

Patients should be instructed to return for follow-up visits only if symptoms persist or recur within 2 months of onset of initial symptoms.

Management of Sex Partners

VVC is not usually acquired through sexual intercourse; treatment of sex partners is not recommended but may be considered in women who have recurrent infection. A minority of male sex partners may have balanitis, which is characterized by erythematous areas on the glans of the penis in conjunction with pruritus or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms.

Special Considerations

Allergy to or Intolerance of the Recommended Therapy. Topical agents usually cause no systemic side effects, although local burning or irritation may occur. Oral agents occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has been associated rarely with abnormal elevations of liver enzymes. Clinically important interactions might occur when these oral agents are administered with other drugs, including astemizole, calcium channel antagonists, cisapride, coumadin, cyclosporin A, oral hypoglycemic agents, phenytoin, protease inhibitors, tacrolimus, terfenadine, theophylline, trimetrexate, and rifampin.

Complicated VVC

Recurrent Vulvovaginal Candidiasis

Recurrent vulvovaginal candidiasis (RVVC), usually defined as four or more episodes of symptomatic VVC each year, affects a small percentage of women (<5%). The pathogenesis of RVVC is poorly understood, and most women who have RVVC have no apparent predisposing or underlying conditions. Vaginal cultures should be obtained from patients with RVVC to confirm the clinical

diagnosis and to identify unusual species, including non-albicans species, particularly Candida glabrata (C. glabrata does not form pseudohyphae or hyphae and is not easily recognized on microscopy). C. glabrata and other non-albicans Candidia species are found in 10%--20% of patients with RVVC. Conventional antimycotic therapies are not as effective against these species as against C. albicans.

Treatment

Each individual episode of RVVC caused by C. albicans responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, specialists recommend a longer duration of initial therapy (e.g., 7--14 days of topical therapy or a 150-mg, oral dose of fluconazole repeated 3 days later) to achieve mycologic remission before initiating a maintenance antifungal regimen.

Maintenance Regimens

Maintenance antifungals are selected on the basis of pharmacologic characteristics of individual agents and route of administration. Recommended regimens include clotrimazole (500-mg dose vaginal suppositories once weekly), ketoconazole (100-mg dose once daily), fluconazole (100--150-mg dose once weekly), and itraconazole (400-mg dose once monthly or 100-mg dose once daily). Although all maintenance regimens should be continued for 6 months, an estimated one in 10,000--15,000 persons exposed to ketoconazole may develop hepatotoxicity. Patients receiving long-term ketoconazole should be monitored for toxicity.

Suppressive maintenance antifungal therapies are effective in reducing RVVC. However, 30%--40% of women will have recurrent disease once maintenance therapy is discontinued. Routine treatment of sex partners is controversial. Although C. albicans azole resistance is rare in vaginal isolates, surveillance of recurrent isolates for development of resistance is prudent.

Severe VVC

Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) has lower clinical response rates in patients treated with short courses of topical or oral therapy. Either 7--14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.

Non-albicans VVC

The optimal treatment of non-albicans VVC remains unknown. Longer duration of therapy (7--14 days) with a non-fluconazole azole drug is recommended as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for 2 weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. Additional options include topical 4% flucytosine; however, referral to a specialist is advised. Safety data regarding the long-term use of these regimens are lacking. If non-albicans

VVC continues to recur, a maintenance regimen of 100,000 units of nystatin delivered daily via vaginal suppositories has been successful.

Compromised Host

Women with underlying debilitating medical conditions (e.g., those with uncontrolled diabetes or those receiving corticosteroid treatment) do not respond as well to short-term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., 7--14 days) conventional antimycotic treatment is necessary.

Pregnancy

VVC often occurs during pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women.

HIV Infection

The attack rate of VVC in HIV-infected women is unknown. Vaginal Candida colonization rates in HIV-infected women are higher than among seronegative women with similar demographic characteristics and high-risk behaviors, and the colonization rates correlate with increasing severity of immunosuppression. Symptomatic VVC is more frequent in seropositive women and similarly correlates with severity of immunodeficiency. In addition, among HIV-infected women, systemic azole exposure is associated with the isolation of non-albicans Candida species from the vagina.

Based on available data, therapy for VVC in HIV-infected women should not differ from that for seronegative women. Although long-term prophylactic therapy with fluconazole at a dose of 200 mg weekly has been effective in reducing C. albicans colonization and symptomatic VVC, it is not recommended for routine primary prophylaxis in HIV-infected women in the absence of RVVC. Given the frequency with which RVVC occurs in the immunocompetent healthy population, RVVC should not be considered a sentinel sign to justify HIV testing.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Throughout the 2002 guideline document, the evidence used as the basis for specific recommendations is discussed briefly. More comprehensive, annotated discussions of such evidence will appear in background papers that will be published in a supplement issue of the journal Clinical Infectious Diseases.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis and management of bacterial vaginosis, trichomoniasis, and vaginal candidiasis
- Treatment of patients and sex partners results in the relief of symptoms, microbiologic cure, and reduction of transmission
- Reduction on the rate of preterm deliveries and other adverse pregnancy outcomes in pregnant women with bacterial vaginosis
- Prevention of transmission of trichomoniasis to sex partners

Specifically:

- The results of one randomized controlled trial indicates that treatment of bacterial vaginosis with metronidazole substantially reduces postabortion pelvic inflammatory disease.
- In randomized clinical trials, the recommended metronidazole regimens have resulted in cure rates of approximately 90-95%. Treatment of patients and sex partners results in relief of symptoms, microbiologic cure, and reduction in transmission.
- Treatment with azoles results in relief of symptoms and negative cultures among 80-90% of patients who complete therapy

Subgroups Most Likely to Benefit:

Treatment of bacterial vaginosis in asymptomatic pregnant women who are at high risk for preterm delivery might prevent adverse pregnancy outcomes.

POTENTIAL HARMS

- Topical agents usually cause no systemic side effects, although local burning may occur. Oral agents occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has been associated rarely with abnormal elevations of liver enzymes. Hepatotoxicity secondary to ketoconazole therapy occurs in an estimated one of every 10,000-15,000 exposed persons. Clinically important interactions might occur when oral agents are administered with other drugs including astemizole, calcium channel antagonists, cisapride, coumadin, cyclosporin A, oral hypoglycemic agents, phenytoin, protease inhibitors, tacrolimus, terfenadine, theophylline, trimetrexate, and rifampin.
- Butoconazole, clotrimazole, miconazole, tioconazole, and terconazole creams and suppositories are oil-based and might weaken latex condoms and diaphragms; refer to condom product labeling for additional information
- Clindamycin cream and ovules are oil-based and might weaken latex condoms and diaphragms; refer to condom product labeling for additional information.

Subgroups Most Likely to be Harmed:

The use of clindamycin cream during pregnancy is not recommended because evidence from three trials suggests an increase in adverse events (e.g., prematurity and neonatal infection).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These recommendations were developed in consultation with public- and private-sector professionals knowledgeable in the treatment of patients with sexually transmitted diseases (STDs). They are applicable to various patient-care settings, including family planning clinics, private physicians' offices, managed care organizations, and other primary-care facilities. When using these guidelines, the disease prevalence and other characteristics of the medical practice setting should be considered. These recommendations should be regarded as a source of clinical guidance and not as standards or inflexible rules. These guidelines focus on the treatment and counseling of individual patients and do not address other community services and interventions that are important in sexually transmitted disease STD/human immunodeficiency virus (STD/HIV) prevention.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2002 May 10;51(RR-6):42-8.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1993 (revised 2002 May 10)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

GUIDELINE DEVELOPER COMMENT

These guidelines for the treatment of patients who have sexually transmitted diseases (STDs) were developed by the Centers for Disease Control and Prevention (CDC) after consultation with a group of professionals knowledgeable in the field of STDs who met in Atlanta on September 26--28, 2000.

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Not stated

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The information in this report updates the "1998 Sexually Transmitted Diseases Treatment Guidelines" (MMWR 1998;47[No. RR-1]).

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- HTML version
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Workowski KA, Levine WC, Wasserheit JN. U.S. Centers for Disease Control and Prevention guidelines for the treatment of sexually transmitted diseases: an opportunity to unify clinical and public health practice. Ann Intern Med. 2002 Aug 20;137(4):255-62. Electronic copies: Available through Annals of Internal Medicine Online.
- Sexually Transmitted Diseases Treatment Guidelines 2002 for PDA or Palm OS. Available from the CDC National Prevention Information Network (NPIN) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 2002.

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